

THE LEWIS ACID-CATALYZED INTRAMOLECULAR ASYMMETRIC
HETERO DIELS-ALDER REACTION OF CHIRAL α' -SULFINYL- α,β -
UNSATURATED KETONE. A CHIRAL DIENE BEARING AN OPTICALLY
ACTIVE SULFINYLMETHYL GROUP†

Kunio Hiroi,* Masayuki Umemura, and Yoko Tomikawa

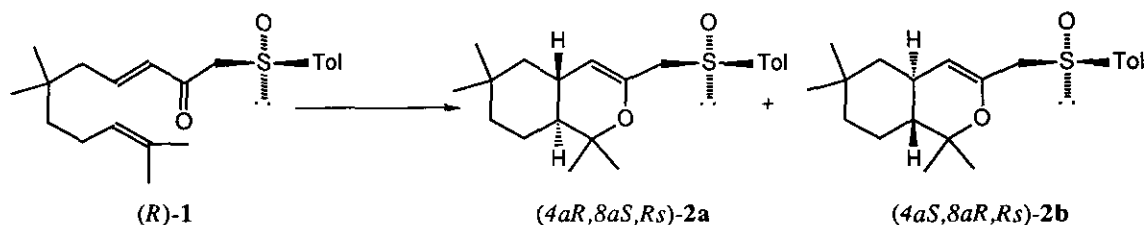
Department of Synthetic Organic Chemistry, Tohoku College of Pharmacy, 4-4-1
Komatsushima, Aoba-ku, Sendai, Miyagi 981, Japan

Abstract — This paper presents an asymmetric Diels-Alder reaction with a diene bearing a chiral sulfinyl group. The Lewis acid-catalyzed intramolecular asymmetric hetero Diels-Alder reaction of a chiral α' -sulfinyl- α,β -unsaturated ketone derived from 3-methylcitronellal produced optically active 4a,5,6,7,8,8a-hexahydro-1H-2-benzopyran derivatives. On the basis of the stereochemical results obtained, a plausible mechanism for the asymmetric induction is presented.

During the past decade asymmetric Diels-Alder reactions have received much attention for the stereoselective construction of cyclic compounds with high enantioselectivity.¹ The known asymmetric Diels-Alder reactions with chiral organosulfur compounds have been limited to intermolecular ones using chiral vinylic sulfoxides² and sulfoximines³ as dienophiles.

We have quite recently reported the first successful example of the intramolecular asymmetric hetero Diels-Alder reaction of a chiral α -sulfinyl- α,β -unsaturated ketone which served as an efficient chiral diene.⁴ We wish to communicate herein another example of the intramolecular asymmetric Diels-Alder reaction with a chiral diene bearing an optically active sulfinylmethyl function. The asymmetric synthesis of 4a,5,6,7,8,8a-hexahydro-1H-2-benzopyrans was achieved by this asymmetric Diels-Alder reaction with a chiral sulfinyl group.

A model compound ((*R*)-**1**), a chiral α' -sulfinyl- α,β -unsaturated ketone, was prepared starting from 3-



† This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

Table I. Studies on the Lewis Acid-catalyzed Intramolecular Asymmetric Hetero Diels-Alder Reactions of (*R*)-1

Lewis acids	Solvent	Reaction conditions ^{a)}		Yields of 2 (%)	d.e. (%) of 2 ^{b)}
		Temp. (°C)	Time (h)		
ZnCl ₂	CH ₂ Cl ₂	0	2	94	40.0
ZnCl ₂	Toluene	0	2	63	48.6
ZnBr ₂	CH ₂ Cl ₂	0	3	47	40.2
ZnBr ₂	Toluene	0	3	75	38.3
Zn I ₂	CH ₂ Cl ₂	0	2	82	44.2
Zn I ₂	Toluene	0	2	82	38.6
Et ₂ AlCl	CH ₂ Cl ₂	-78	1	84	42.5
Et ₂ AlCl	Toluene	-78	1	100	28.5
Et ₂ AlCl	Hexane	room temperature	18	48	34.7
EtAlCl ₂	CH ₂ Cl ₂	-78	2	72	38.5
EtAlCl ₂	Toluene	-78	1	82	35.8
AlCl ₃	CH ₂ Cl ₂	-78	2	77	29.0
AlCl ₃	Toluene	-78	2	54	38.0
Me ₃ Al	CH ₂ Cl ₂	-78	1	61	18.5 ^{c)}
FeCl ₃	CH ₂ Cl ₂	0	2	42	44.8
FeCl ₃	Toluene	0	1	68	36.6
TiCl ₄	CH ₂ Cl ₂	-78	1	85	31.7
SnCl ₄	CH ₂ Cl ₂	-78	1	82	45.4
SnCl ₄	Toluene	-78	1	81	60.6
BF ₃ ·OEt ₂	CH ₂ Cl ₂	0	2	74	15.2 ^{c)}
BF ₃ ·OEt ₂	Toluene	0	2	70	3.0 ^{c)}

a) The reactions of (*R*)-1 were carried out in the presence of the Lewis acids (1.5 equiv.).

b) The diastereomeric excess (d.e.) of 2a over 2b was determined by the hplc analysis.

c) The compound (4*aS*,8*aR*,*Rs*)-2b was obtained as a main product.

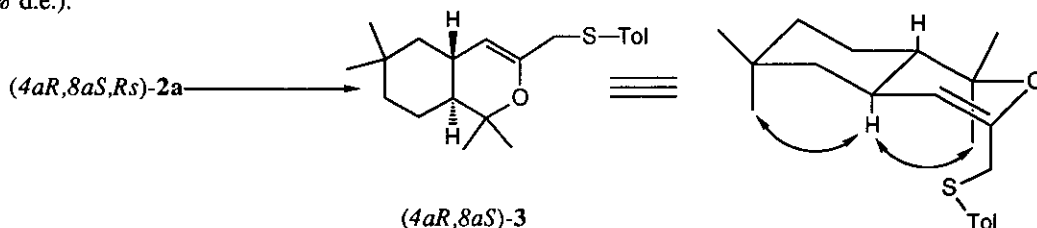
methylcitronellal⁵ in the following sequence. The Horner-Emmons condensation of ethyl diethoxyphosphinylacetate with 3-methylcitronellal at 0 °C for 1 h using sodium hydride as a base gave ethyl 5,5,9-trimethyl-2(*E*),8-decadienoate in 87% yield. The condensation of the (*R*)-methyl *p*-tolyl sulfoxide⁶ carbanion with the ester carbonyl group at 0 °C for 1 h afforded the model compound ((*R*)-1) in 64% yield.

The Lewis acid-catalyzed reactions of (*R*)-1 were carried out in dichloromethane, toluene, or hexane at -78 °C ~ 0 °C to produce optically active hetero Diels-Alder reaction products, (4*aR*,8*aS*,*Rs*)- and (4*aS*,8*aR*,*Rs*)-4*a*,5,6,7,8,8*a*-hexahydro-1,1,6,6-tetramethyl-2-*p*-toluenesulfinylmethyl-1*H*-2-benzopyran (2a) and (2b), along with no ene reaction product.^{4,7} The results obtained by using various Lewis acids are summarized in Table I. The ratios of the diastereomer 2a to 2b were determined by the high-performance liquid chromatographic (hplc) analysis and listed in Table I.

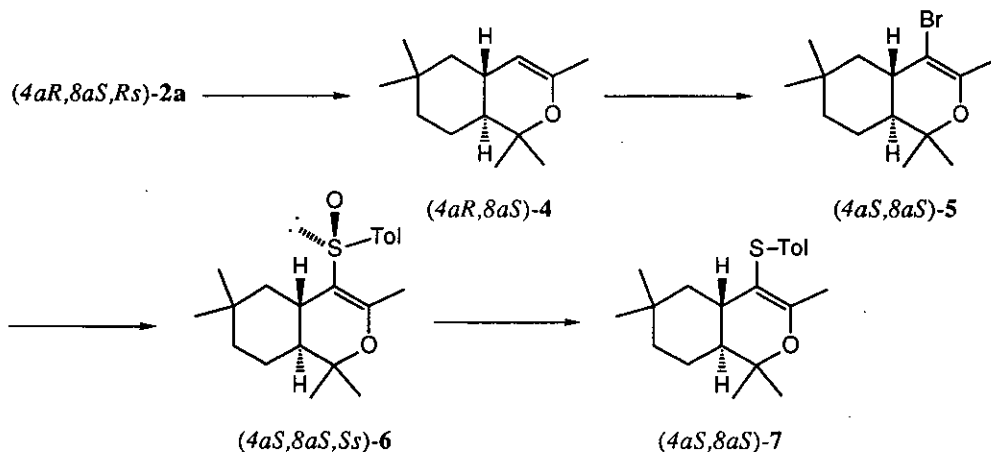
Use of zinc(II) chloride, bromide, and iodide, diethylaluminum chloride, ethylaluminum dichloride, and aluminum(III) chloride, iron(III) chloride, or titanium(VI) chloride as a Lewis acid catalyst furnished the hetero Diels-Alder reaction products (2a,b) with moderate or rather low diastereomeric excess of 2a over 2b. The highest diastereomeric excess (60.6 %) of 2a was observed on the use of tin(IV) chloride in toluene at -78 °C.

However, the opposite diastereoselectivity of **2a,b** was found on the use of boron trifluoride etherate and trimethylaluminum with very low diastereomeric excess of **2b** over **2a**. No cycloaddition product was obtained under the thermal reaction conditions (refluxed in toluene for 48 h).

The stereochemistry of the products (**2a,b**) was confirmed as *trans* configuration by the observation of the nuclear Overhauser effects (NOE) between the C_{4a} hydrogen atom and the methyl groups at the C₁ and C₆ positions in the nmr spectral analysis of the sulfide ((*4aR,8aS*)-**3**) ([α]_D +15.0° (c=1.33, CHCl₃), 39 % e.e.) obtained by the TiCl₃ reduction of the sulfinyl function in (*4aR,8aS,RS*)-**2a** ([α]_D +130.4° (c=2.50, CHCl₃), 39 % d.e.).



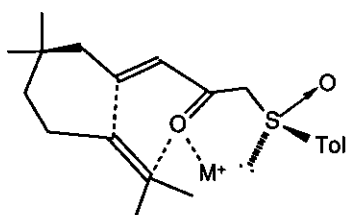
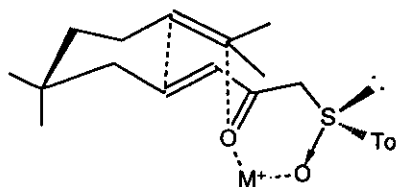
The absolute configuration of the newly created asymmetric two carbons in the hetero Diels-Alder product (**2a,b**) was determined by the chemical correlation to the chiral sulfinyl compound (**6**) of the known absolute configuration⁴ as follows. The reductive desulfinylation of the chiral sulfoxide (**2a**) ([α]_D +130.4° (c=2.50, CHCl₃), 39 % d.e.) with sodium was carried out in *iso*-propanol-tetrahydrofuran (THF)⁸ at room temperature for 2 h to give (*4aR,8aS*)-**4a,5,6,7,8,8a**-hexahydro-1,1,3,6,6-pentamethyl-1*H*-2-benzopyran (**4**) ([α]_D +22.0°



(c=3.65, CHCl₃)) in 90 % yield. The bromination of the cyclic enol ether (**4**) with *N*-bromosuccinimide in THF-H₂O (4:1) at room temperature for 3 h gave an α -bromo cyclic enol ether ((*4aS,8aS*)-**5**) ([α]_D -14.2° (c=1.76, CHCl₃)) in 32 % yield. After treatment of the vinylic bromide ((*4aS,8aS*)-**5**) with *n*-butyllithium at -78 °C in THF, the sulfinylation reaction of the carbanion generated with methyl (*S*)-*p*-toluenesulfinate (87 % e.e.) at -78 °C for 2 h produced a 67 : 33 mixture of the known chiral sulfinyl compounds ((*4aS,8aS,SS*)-**6a**⁴ ([α]_D -106.2° (c=0.87, CHCl₃))) and ((*4aR,8aR,SS*)-**6b**⁴ ([α]_D +83.1° (c=0.67, CHCl₃))), respectively, in 32%

yield. The reduction of the sulfinyl groups in $(4aS,8aS,5S)$ -**6a** and $(4aR,8aR,5S)$ -**6b** with TiCl_3 in THF at room temperature furnished the known chiral sulfenyl compound, $((4aS,8aS)$ -(-)-**7**⁴ ($[\alpha]_D -30.6^\circ$ ($c=1.93$, CHCl_3))) and $((4aR,8aR,5S)$ -(+)-**7**⁴ ($[\alpha]_D +27.5^\circ$ ($c=1.56$, CHCl_3))) in 88 % yield, respectively. Thus, the absolute configuration of the newly created two asymmetric carbons in **2a** and **2b** formed by this hetero Diels-Alder reaction was determined as $(4aR,8aS)$ and $(4aS,8aR)$, respectively.

The mechanism for the asymmetric induction in this hetero Diels-Alder reaction was rationalized on the basis of the stereochemical results obtained as follows. The intramolecular cycloaddition of the olefin to the α,β -unsaturated ketone in (R) -**1** would occur preferentially from the direction of the same downward side as the less hindered lone pair of the chiral sulfinyl group in the most preferred conformation (**8a**) formed by the dipole-dipole repulsion between the carbonyl group of the ketone and the sulfinyl sulfur-oxygen bond, yielding $(4aR,8aS,5S)$ -**2a** as a main product. On the use of boron trifluoride etherate or trimethylaluminum as a catalyst, the compound $((4aS,8aR,5S)$ -**2b**) would be formed, with slight diastereomeric excess, by the predominant intramolecular cycloaddition of (R) -**1** from the direction of the same upward side as the less hindered lone pair of the chiral sulfinyl group in the six-membered transition state (**8b**) formed by the chelation of the Lewis acid with the carbonyl oxygen and the sulfinyl oxygen.

**8a****8b**

Thus, the chiral α' -sulfinyl- α,β -unsaturated ketone was demonstrated to serve as a good chiral diene in the Lewis acid-catalyzed reaction to provide the asymmetric hetero Diels-Alder adducts with high stereoselectivity. This method provided an alternative way to optically active cyclic enol ethers by the effect of the chirality of the optically active sulfinyl groups.

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